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EXAMINER	
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ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,998	COOL ET AL.	
	Examiner	Art Unit	
	RONALD T. NIEBAUER	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-8,12-16 and 19* is/are pending in the application.

4a) Of the above claim(s) *15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-8,12-14,16,19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/27/10 has been entered.

Applicants arguments and amendments filed 12/18/09 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed is herein withdrawn. Briefly, the amendments have overcome the previous 112 2nd rejection of claim 12, and the 102b rejection based on Hudson, and the 103 rejection based on Mihala and Thaler.

Previously, (9/30/08) applicants elected a benzyltrimethylammonium salt and Fmoc protecting group. In the instant case, each of the elected species was found in the prior art or found to be obvious based on the prior art. Any art that was uncovered in the course of searching for the elected species that reads on non-elected species is also cited herein. In accord with section 803.02 of the MPEP, the Markush-type claims have been examined with respect to the elected species and to the extent necessary to determine patentability.

Since applicant elected Fmoc, claims 14-15 do not read on the elected species. Since the art reads on claim 14 it is included in this rejection.

Claim 15 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 9/30/08.

Claims 1-2,9-11,17-18 have been cancelled.

Claims 3-8,12-14,16,19 are under consideration.

Claim Rejections - 35 USC § 112

This rejection is a new rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 depends from claim 16 which depends from claim 3. Claim 19 refers to steps a) and b). However both claims 3 and 16 recite steps a) and b). Claim 3 recites that step b) is perform a thorough washing. Claim 16 recite that step b) is perform the process according to claim 3. As such, it is unclear if claim 19 is referring to steps a) and b) of claim 3 or 16. There is more than one reasonable interpretation of the claim – that steps a) and b) are the steps as recited in claim 3 or that that steps a) and b) are the steps as recited in claim 16.

Claim Rejections - 35 USC § 102

A rejection based on Birr appeared in the previous office action. An updated rejection appears below.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 3-5,14,16,19 are rejected under 35 U.S.C. 102(b) as being anticipated by Birr (US 4,290,943, first cited 10/27/09).

Birr teach methods of preparing polypeptides (abstract). Birr teach that peptides are prepared by solid phase technique (column 1 line 47-50). Birr specifically teach that the N-terminal protective group is removed (column 5 line 19-22), a wash is performed (column 5 line 29-30), and the next N-terminally protected amino acid is coupled (column 5 line 30-32). In a specific example (columns 6-8) Birr teach that benzyltrimethylammonium hydroxide (in methanol and dioxane) is used to cleave off a peptide fragment (column 7 lines 34-36).

Since Birr teach a solid phase technique (column 1 line 47-50) in which the N-terminal protective group is removed (column 5 line 19-22), a wash is performed (column 5 line 29-30), and the next N-terminally protected amino acid is coupled (column 5 line 30-32) steps a-c/a-d of claims 3-5 are met. Since Birr teach that benzyltrimethylammonium hydroxide (in methanol and dioxane) is used to cleave off a peptide fragment (column 7 lines 34-36) a salt is used in the process and the salt meets the limitations as recited in claims 3,5 of the instant claims. Thus Birr teach that the salt is used during the cleavage of the peptide as recited in claim 3a,5a. Birr teach a specific example (columns 6-8) in which a peptide is synthesized and cleaved (column 7 lines 25-36), thus the limitations of claim 16 are met. Birr teach (column 4 lines 11-19, column 7 line

25) thus use of the amino protecting group Ddz which is described as acid-labile (column 4 lines 11-19) as recited in claim 14.

It is noted that the claims state that the washing is 'thorough'. 'Thorough' is defined (page 2 of specification) as effective to remove reagents from the previous step. Since Hudson teach effective synthesis of peptides (see example 3 columns 9-10) the washings are necessarily thorough to allow for effective synthesis.

Although unclear (see 112 2nd) claim 19 has been interpreted such that the steps of claim 18 can be the steps of claim 3 or 16. In the instant case, the wash step as described by Birr (column 5 line 29-30) meets the limitations of claim 3b and there is not a wash step between step a and b as recited in claim 16. Thus the limitations of claim 19 are met.

Response to Arguments 102 rejection

A rejection based on Birr appeared in the previous office action. An updated rejection appears above. Applicants arguments will be considered to the extent that they apply to the current rejection and claim set.

Applicants argue (page 7-8) that Birr does not teach any salts other than benzyltrimethylammonium hydroxide.

Applicants argue that Birr does not teach the use of a salt in steps a,b, or c of the instant claims.

Applicant's arguments filed 12/18/09 have been fully considered but they are not persuasive.

Although Applicants argue (page 7-8) that Birr does not teach any salts other than benzyltrimethylammonium hydroxide, it is noted that instant claim 3 expressly recites

benzyltrimethylammonium hydroxide as a salt which is the salt taught by Birr. Claim 3 does not require the use of multiple salts.

Although Applicants argue that Birr does not teach the use of a salt in steps a,b, or c of the instant claims, claim 3a refers to cleaving the alpha-amino protecting group OR the peptide attached to the support. Thus claim 3a refers to cleaving either the alpha-amino protecting group or the peptide itself. The use of the word 'or' is evidence of alternate elements being cleaved. In the instant case, Birr expressly teach cleaving the peptide that is attached to the support (column 7 lines 34-36) as recited in the instant claim.

The rejection based on Merrifield is a new rejection.

Claims 3-4,7,14,16,19 are rejected under 35 U.S.C. 102(b) as being anticipated by Merrifield et al (J Org Chem 'The limits of reaction of radioactive dicyclohexylcarbodiimide with amino groups during solid-phase peptide synthesis' v42 (1977) pages 1291-1295) as evidenced by Finger (US 4,218,400).

Merrifield teach solid-phase peptide synthesis (title). Merrifield teach (abstract) the use of a quaternary ammonium hydroxide during peptide synthesis. Merrified teach (page 1293 section 'acylation') that a resin bound peptide prepared by solid phase synthesis was reacted with Boc-Ala in the presence of Triton B. Merrifield teach (page 1293 section 'acylation') that the Triton B enables the chemical reaction. Merrifield teach (page 1294 section 'acylation of amidino peptide resins') that the product was cleaved from the resin and identified using chromatography.

Merrified teach that Triton B is a quaternary ammonium hydroxide, but does not disclose the exact structure of Triton B. Finger (US 4,218,400) teach (column 2 lines 9-11) that Triton B is benzyl-trimethyl-ammonium hydroxide.

Since Merrifield teach solid-phase peptide synthesis steps a-c of claims 3,7 are carried out. For example, Merrifield teach deprotection and washing (page 1294 section 'reaction of DCC with HCl-Gly-Resin and Gly-Resin') as in steps a-b of claims 3,7. Merrifield teach that Boc-Ala an amino protected amino acid was added as in step c of claims 3,7. Since Merrifield teach Boc the limitations of claim 14 are met. Since Merrifield teach that benzyl-trimethyl-ammonium hydroxide (i.e. Triton B) was used during the Boc-Ala addition a salt as recited in claims 3,7 was used in step c of claims 3,7. Since Merrifield teach that products were analyzed (page 1294 section 'reaction of DCC with HCl-Gly-Resin and Gly-Resin') an additional washing step occurred in order to retrieve the products as recited in claim 4. Since Merrifield teach solid-phase peptide synthesis of a specific peptide (page 1293 section 'acylation') and teach cleavage to obtain the products (page 1294 section 'acylation of amidino peptide resins') the limitations of claim 16 are met.

It is noted that the claims state that the washing is 'thorough'. 'Thorough' is defined (page 2 of specification) as effective to remove reagents from the previous step. Since Merrifield teach effective synthesis of peptides and analysis of products the washings are necessarily thorough to allow for effective synthesis.

Although unclear (see 112 2nd) claim 19 has been interpreted such that the steps of claim 18 can be the steps of claim 3 or 16. In the instant case, Merrifield teach washing (page 1294

section 'reaction of DCC with HCl-Gly-Resin and Gly-Resin') as in steps a-b of claims 3,7. Thus the limitations of claim 19 are met.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3-8,12-14,16,19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rink (US 5,004,781) and Mihala et al (Journal of Peptide Science 'An alternative solid phase peptide fragment condensation protocol with improved efficiency' 7:565-568 (2001), cited in previous office action) and Merrifield et al (J Org Chem 'The limits of reaction of radioactive dicyclohexylcarbodiimide with amino groups during solid-phase peptide synthesis' v42 (1977) pages 1291-1295) and Finger (US 4,218,400).

Rink teach that the Merrifield synthesis of peptidic compounds is known (column 1 lines 43-column 2). Rink teach that the process includes the removal of an N-terminal protecting group (column 1 lines 51-52), another amino acid is added until the desired sequence is obtained (column 1 lines 62-64), and the peptide is removed from the support (column 1 lines 53-54). In the examples, Rink teach that there are wash steps after the cleavage and coupling steps (column 14 lines 24-41). Rink recognizes the use of Fmoc as a protecting group (column 8 line 42 , example 6). Rink teach (column 5 lines 7-25) that benzyltrimethylammonium hydroxide, for example, can be used to remove the amino protecting group. Rink expressly teach that the use of benzyltrimethylammonium hydroxide can be carried out at lower temperatures and can be concluded after a much shorter reaction time.

Although Rink refer to the use of benzyltrimethylammonium hydroxide, Rink does not expressly use benzyltrimethylammonium hydroxide in a specific example. Rink does not teach the use of benzyltrimethylammonium hydroxide at any and all steps of the process.

Rink recognizes some of the challenges of solid phase peptide synthesis including the difficulties in synthesizing longer peptides (column 2 lines 28-30) and problems with selectively detaching the peptide from the support (column 2 lines 23-27). Thus one would be motivated to address these known problems.

Mihala also teach solid phase peptide synthesis (title). Like Rink, Mihala recognizes that the problems with synthesizing long peptides includes decreasing solubility and associations (via van der Waals and hydrogen bonding) between the peptide chains (page 565 first paragraph). Mihala teach that the success of solid phase synthesis is limited by the aggregation of the

growing peptide chains (abstract, page 565). Mihala teach that protected amino acids (page 566 section 'general') were used and that coupling steps were carried out with tetrabutyl ammonium salt additive (TBA*ODhbt) (page 566 section 'solid phase synthesis'). Mihala teach that the tetrabutyl ammonium salt additive is used to enhance solubility (page 567 first complete paragraph). Mihala teach that the tetrabutyl ammonium salt additive lead to improved efficiency (title, abstract, Table 1). Mihala suggests that use of the ammonium salt as an additive provides an alternative for improving coupling efficiency in solid phase peptide synthesis (last paragraph page 567). Further, it is noted that the art recognizes the use of salts in many column purification and other separation strategies for improved separation.

Taken together, both Rink and Mihala teach peptide synthesis and the use of ammonium salts during the process. Rink teaches an ammonium salt for the cleavage steps and Mihala teach an ammonium salt to enhance solubility and prevent aggregation. Since aggregation can be a problem at all steps of the process one would be motivated to enhance solubility throughout the process.

Merrifield also teach solid-phase peptide synthesis (title). Merrifield teach (abstract) the use of an ammonium salt (quaternary ammonium hydroxide) during peptide synthesis. Merrifield teach (page 1293 section 'acylation') that a resin bound peptide prepared by solid phase synthesis was reacted with Boc-Ala in the presence of Triton B. Merrifield teach (page 1293 section 'acylation') that the Triton B enables the chemical reaction. Merrifield teach (page 1294 section 'acylation of amidino peptide resins') that the product was cleaved from the resin and identified using chromatography. Merrified teach that Triton B is a quaternary ammonium hydroxide, but does not disclose the exact structure of Triton B. Finger (US 4,218,400) teach

(column 2 lines 9-11) that Triton B is benzyl-trimethyl-ammonium hydroxide. Thus Merrifield teach the use of an ammonium salt during the addition step of the synthesis.

Taken together, Rink and Mihala and Merrifield teach peptide synthesis and the use of ammonium salts during the process. Rink teaches an ammonium salt for the cleavage steps and Mihala teach an ammonium salt to enhance solubility and prevent aggregation. Since aggregation can be a problem at all steps of the process one would be motivated to enhance solubility throughout the process. Merrifield teach that an ammonium salt enables the chemical reaction for the synthesis.

Rink teach the basic steps of solid phase synthesis. Rink teach that the process includes the removal of an N-terminal protecting group (column 1 lines 51-52), another amino acid is added until the desired sequence is obtained (column 1 lines 62-64), and the peptide is removed from the support (column 1 lines 53-54). In the examples, Rink teach that there are wash steps after the cleavage and coupling steps (column 14 lines 24-41). Thus Rink teach steps a-d of claims 3-8. Since Rink teach that another amino acid is added until the desired sequence is obtained (column 1 lines 62-64), and the peptide is removed from the support (column 1 lines 53-54) Rink teach the steps as in claim 16. Rink recognizes the use of Fmoc as a protecting group (column 8 line 42 , example 6) as in claim 13 and Boc (example 6) as recited in claim 14. Rink motivate the use of benzyltrimethylammonium hydroxide (column 5 lines 7-25) during the cleavage step since it allows for a lower reaction temperature and shorter reaction time. Thus, Rink teach a salt as recited in the instant claims. One would be motivated to include benzyltrimethylammonium hydroxide in the cleavage step (step a of the instant invention) as recited in claims 3,5. One would have a reasonable expectation of success since Rink expressly

suggest the use of benzyltrimethylammonium hydroxide in the cleavage step and state that it allows for a lower reaction temperature and shorter reaction time. Since Rink recognizes that one of the challenges of solid phase peptide synthesis including the difficulties in synthesizing longer peptides (column 2 lines 28-30) one would be motivated to use the teachings of Mihala who teach that an ammonium salt additive is used to enhance solubility (page 567 first complete paragraph). Since Rink already teach the use of an ammonium salt one would be motivated to use the specific salt as taught by Rink. One would have a reasonable expectation of success based on the teachings of the references. Since solubility and aggregation are potential problems at various stages one would be particularly motivated to include the salts during the washing steps as recited in claims 6,8,12. Further, since Merrifield teach (page 1293 section 'acylation') that Triton B (i.e. benzyltrimethylammonium hydroxide) enables the chemical reaction one would be motivated to use the benzyltrimethylammonium hydroxide during the addition steps as recited in claim 7. One would have a reasonable expectation of success based on the express teachings of Merrifield.

In summary, Rink Mihala and Merrifield all teach the well-known solid phase peptide synthesis technique. The references teach advantages of including salts specifically ammonium salts at various stages of the process. Rink teach (column 5 lines 7-25) that benzyltrimethylammonium hydroxide can be used to remove the amino protecting group. Rink expressly teach that when benzyltrimethylammonium hydroxide is used that the cleavage can be carried out at lower temperatures and can be concluded after a much shorter reaction time. Merrifield also teach the use of benzyltrimethylammonium hydroxide, specifically during the addition step to enable the chemical reaction (page 1293 section 'acylation'). Further, Mihala

addresses the problem of aggregation by using an ammonium salt to increase solubility and decrease aggregation. Since the references show that the art recognizes the use of ammonium salts as additives at various stages of the peptide synthesis process one would have a reasonable expectation of success.

It is noted that the claims state that the washing is 'thorough'. 'Thorough' is defined (page 2 of specification) as effective to remove reagents from the previous step. Since Rink teach effective synthesis of peptides and analysis of products the washings are necessarily thorough to allow for effective synthesis.

Although unclear (see 112 2nd) claim 19 has been interpreted such that the steps of claim 18 can be the steps of claim 3 or 16. In the instant case, Rink teach washing (column 14 lines 24-41) as in steps a-b of claims 3,7. Thus the limitations of claim 19 are met.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RONALD T. NIEBAUER whose telephone number is (571)270-3059. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, alt. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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